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Editorial

ALTERNATIVE TO ANTIBIOTICS - PREPARATION FOR POST ANTIBIOTIC ERA

All the living entities of our planet are struggling continuously for their existence. Starting from the minute viruses, the fungus, bacteria, protozoa, parasites, plants and animals of various differentiated species are struggling for their existence and multiplication. In the way of such struggle, as a part of evolution, many microorganisms developed their system to secrete some antibacterial chemicals which are identified by some scientists and used as antibiotics. Due to uncontrolled use of these chemicals, the susceptible organisms get ample opportunity to alter their old systems and to develop some new system to bypass the detrimental effect of those chemicals. It is called microbial resistance. In many cases, that power of resistance is transmissible vertically among the same species and horizontally between other species of organisms (Pattanayak 2011). That ultimately causes some very serious problems like development of Superbugs-organisms resistant to all available antibiotics. Those are becoming a threat to the human civilization!

As man is the most intelligent species of the globe and wants to use all the resources for existence and multiplication of their own species, there is always a pressure to find out the means to overcome anything against such targets. To combat the problems of antibiotic resistance and for searching of alternatives of antibiotic use, various studies are going on throughout the world. The studies can be categorized in some groups.

i) Alteration and/or addition of some new chemicals with the presently available anti microbial substances to bring back their potency.
ii) Searching of some new means of attack on harmful micro organisms by use of other microorganisms or their products.
iii) Acceleration of immunity power of human or animals by using the tools present in the microorganisms.
iv) Use of some new types of substances and procedures against microorganisms which were not previously used.
v) Use of antimicrobial, immune-stimulant and other related substances developed in higher species through evolution.

i) Alteration and/or addition of some new chemicals with the presently available antimicrobial substances to bring back their potency.

Penicillins were the first group of antibiotic, and resistance against that group of antibiotic noticed first. The resistant microbes produced beta lactamase enzymes for that purpose. To overcome the problem, some chemicals (Clavulanic acid, Sulbactam, Tazobactam etc.) were added with that group of antibiotics. These chemicals are not having any anti-microbial action, but these can assist the antibiotics to overcome the resistance of the microbes. Afterwards, some other ways were searched out (bacterial efflux inhibition agents, use of analogue of antibiotics etc.) to overcome the resistance of the microorganisms (Pattanayak 2011). But ultimately it remains a common trend that after effective use for a few years, the efficacy of these alterations becomes reduced gradually due to the modification of resistance mechanism of the micro organisms. So, even continuous searching and development of such chemicals as well as prolongation of life of presently used antimicrobials, the actual efficacy of such procedures becoming shorter lasting day by day.

ii) Searching of some new means of attack on harmful microorganisms by use of other micro organisms or their products.

Antimicrobial peptides: Various plants, animals and fungi have vastly different immune systems, but all make peptides (small proteins) that can destroy bacteria. Many amphibian and reptile species developed peptides which can kill many pathogenic microorganisms. These peptides are under study for their therapeutic use as effective anti-microbial agents (Readon 2015).

The host defense peptides (small, natural peptides) and innate defense regulators (small, synthetic peptides) have indirect antimicrobial effects. They primarily act by increasing expression of anti-inflammatory chemokines and cytokines, and reducing the expression of pro-inflammatory cytokines. The anti-biofilm peptides

specifically inhibit bacterial biofilm formation have been identified and are in preclinical developmental stage. (Czaplewski *et al.* 2016).

Phage therapy: Phases are the viruses that can attack and kill bacteria. Study to use the efficacy of such viruses therapeutically against pathogenic bacteria is very old. As each type of phase generally attacks only one type of bacterium, so during clinical use all the other harmless bacteria left unharmed. As phages are abundant in nature, researchers assume to get ready replacements for any therapeutic strain that bacteria evolve to resist.

Phages secrete enzymes (lysins) to destroy the cell wall of a target bacterium and are potential replacements for antibiotics because of their direct antibacterial action, and as adjuncts because they act to reduce bacterial burden, weaken biofilms, or both. Research shows that lysins are more active against Gram-negative pathogens. Studies on the therapeutic efficacy of Wild-type bacteriophages as well as Genetically Engineered bacteriophages are going on (Czaplewski *et al.* 2016).

Bacteriocins: These are some toxins produced by microbes to inhibit the growth of similar or closely related bacteria. Bacteriocins are structurally, functionally and ecologically very diverse in nature. These can exhibit significant potency against other bacteria (including antibiotic-resistant strains), are stable and can have narrow or broad-spectrum activity. Bacteriocins can even be produced *in situ* in the gut by probiotic bacteria to combat intestinal infections (Cotter *et al.* 2013). The main bacteriocins identified from gram negative bacteria are Microcins, Colicin-like bacteriocins and Tailocins. The gram-positive bacteria derived bactericins are classified into various groups according to their size and some other characters. Nisin and other Lantibiotics are grouped under Class I. The heat stable Class II group includes a subgroup which is having very good potential for use in the field of food preservation and medical applications. Example of that subgroup is Pediocin PA-1 (Heng *et al.* 2007). Other main bacteriocins of other subgroups are Lactococcin G (Nissen-Meyer *et al.* 2009), Enterocin AS-48, Aureocin A53 (Netz *et al.* 2002), Aureocin A70 (Netz *et al.* 2001). Lysostaphin is a representative bacteriocin of Class III type (Bastos *et al.* 2010); Sublancin and Glycocin F belong to the complex type IV bacteriocin (Oman *et al.* 2011, Stepper *et al.* 2011).

iii) Acceleration of immunity power of human or animals by using the tools present in the micro organisms.

Use of antibody: Antibodies that bind to and inactivate a pathogen, its virulence factors, or its toxins were widely considered one of the alternative approaches most likely to have major clinical impact. Antibodies are considered as safe or low risk measure with a high degree of technical feasibility (Czaplewski *et al.* 2016).

Immune Stimulation: Successful antimicrobial therapy depends on impose of an appropriate immune response. Immune stimulation may be considered as a potential adjunct approach along with antibiotic therapy.

Orally used bacterial extracts are used to reduce the incidence of respiratory tract infections in some at-risk groups. Further clinical trials to substantiate their efficacy in other populations would encourage wider use. The mechanisms by which these extracts might work are unclear. Targeted interventions could be devised once these mechanisms are understood. New focused research also has been initiated on assessment of repurposed drugs for immune stimulation rather than assessment of early translational research in this specialty (Czaplewski *et al.* 2016).

Vaccination: From the time of Edward Jenner and Luis Pasteur, research related with immunization of human or animals against serious disease-causing microbes are going on with a history of huge success. The immunization procedures depend on some basic principles. It is achieved by introducing live, generally attenuated infectious agents or inactivated agents or their constituents or their products in the living body so that body protective mechanism can develop power to resist the attack of the original pathogenic micro organisms in future (Harrison 2008). But anybody can not be made immunized against each and every type of organisms which can cause disease by that method.

The long established investment in vaccines for new targets should continue to substantially reduce the incidence of infection and the need for antibiotics (Czaplewski *et al.* 2016).

iv) Use of some new types of substances and procedures against micro organisms which were not previously used.

CRISPR: It is a gene-editing technique based on a strategy that many bacteria use to protect themselves against phages. Researchers are turning that system back on itself to make bacteria kill themselves.

Normally, the bacteria detect and destroy invaders such as phages by generating a short RNA sequence that matches a specific genetic sequence in the foreign body. This RNA snippet guides an enzyme called Cas 9 to kill the invader by cutting its DNA.

Scientists are now designing CRISPR sequences that

target genomes of specific bacteria, and some are aiming their CRISPR kill switches at the bacterial genes that confer antibiotic resistance (Readon 2015).

Metals: Metals like copper and silver are the oldest antimicrobials. They were favored by Hippocrates in the fourth century BC as a treatment for wounds, and were used even earlier by ancient Persian kings to disinfect food and water. In the contemporary research, some groups are exploring the use of metal nanoparticles as antimicrobial treatments. Because metals accumulate in the body and can be highly toxic, their use may be restricted mostly to topical ointments for skin infections.

An exception is gallium, which is toxic to bacteria that mistake it for iron, but is safe enough in people to be tested as an intravenous treatment for lung infections. Pilot studies found that the metal was moderately successful at breaking down microbial biofilms in the lungs and improving patients' breathing (Readon 2015).

Probiotics: Probiotics are some selected microorganisms administered orally. These can confer a health benefit to the host when administered in adequate amounts. A defined mixture of bacteria or the use of non-toxigenic spores of *Clostridium difficile* may provide therapeutic and prophylactic therapies that can improve current clinical practice for the treatment of *C. difficile* associated diarrhea and antibiotic-associated diarrhoea (Czaplewski *et al.* 2016).

Other related studies:

Immune suppression: Bacterial infection can lead to an excessive host innate immune response (ranging from the systemic inflammatory response syndrome to septic shock), in which the injury to the host is made much worse by the host's pro-inflammatory cytokine response. Selective manipulation of this cytokine response could potentially be used in combination with antibiotics to reduce pathogen-induced tissue damage.

Anti-resistance nucleic acids: Antibiotic resistance genes are often spread by highly transmissible plasmids, particularly in Gram-negative pathogens. Effective removal of resistance genes could sensitize bacteria to conventional antibiotics.

Antibacterial nucleic acids: Use of nucleic acids to directly kill bacteria is being investigated in both academia and biotechnology companies. Studies are at an early stage. At the very least, these methods will continue to be developed to support fundamental microbial genetics studies.

Toxin sequestration using liposomes: Pathogens often secrete toxins that damage mammalian cells and cause inflammation. Administration of liposomes to act as decoys for toxin binding has been shown to reduce damage to cells and reduce disease severity.

Antibiotic-degrading enzymes to reduce selection of resistance: When antibiotics are eliminated via the gut, exposure of the normal gut bacteria to the antibiotic may lead to development of resistance and drive *Clostridium difficile* associated diarrhea or antibiotic associated diarrhea. Studies showed that oral β-lactamase can destroy β-lactams in the faeces. Demonstration of a clinical benefit of degrading enzyme administration may be challenging to the process.

Metal chelation: Bacterial pathogens need zinc, manganese, and iron ions to fully express their pathogenicity or virulence, biofilm formation, and multiple essential enzymatic and metallo-β-lactamase activities. Metal chelation could prevent these key processes in pathogens (Czaplewski *et al.* 2016).

Alphamers: Alphamers are immune modifiers consisting of a galactose-∝- 1,3-galactosyl-β-1,4-N-acetyl-glucosamine (Gal) epitope fused to a bacterial pathogen binding aptamer to redirect endogenous anti-Gal antibodies to the pathogen and enhance immune clearance.

Alphamer technology is based on chemically synthesized molecules redirecting naturally occurring antibodies to selected pathogens to fight infection. One end of the molecule binds a surface target of a pathogen cell using an aptamer, while the other end represent specific epitopes that attach the circulating antibodies.

Immune stimulation by P4 peptide: Phagocytic killing of bacteria can be enhanced by P4 peptide - a chemically synthesized 28 amino acid peptide derived from the *Streptococcus pneumoniae* surface exposed virulence factor PsaA. P4 peptide stimulates opsono-phagocytic uptake and killing in invasive disease models of *S. pneumonia* infection in mice. The combination of P4 given intra-nasally and IgG given intra-peritoneally resulted in 100% survival in the mouse model and significantly reduced bacterial burden. A therapy based on P4, IgG and antibiotic may be an effective treatment schedule in future (Czaplewski *et al.* 2016).

Predatory bacteria: Predatory bacteria can be used to control other pathogenic bacteria. Many different types of predatory bacteria have been identified, but the Bdellovibrio and like organisms (BALOs) show particular

promise. BALOs are motile Deltaproteobacteria that obligately predate Gram-negative bacteria for energy and nutrients.The genomes of many BALOs encode numerous hydrolases (e.g., DNases and proteases), essential for prey digestion and sufficient for attacking even bacterial biofilms. It is very important because biofilms pose a treatment challenge in both human and animal infections making bacteria less sensitive to antibiotics (Allen *et al.* 2014).

v) Use of antimicrobial, immune-stimulant and other related substances developed in higher species through evolution.

Presently, almost same types of antimicrobial drugs are used during treatment of various animals as well as in fishery, horticulture and other related purposes. This practice requires re-thinking. Use of antimicrobial drugs may be substituted at least partially for treatment of herbivorous animals by using juice and pieces of succulent part of medicinal plants directly (Pattanayak *et al.* 2016).

Apart from the golden treasury of texts of various ancient Indian systems of medicines, many plants and their different types of extracts, natural products etc. were recommended for their anti-microbial effects in various texts and practices throughout the world. Use of plants for antimicrobial, immune-stimulant and other related purposes are reviewed by many authors. Plants used in/ as tissue and wound healing (42 plants - Jaiswal *et al.* 2004, 36 plants - Pattanayak *et al.* 2013), antiseptic property (35 plants - Pattanayak *et al.* 2013) skin infection (175 plants - Gupta *et al.* 2010), immune-stimulant effect (13 plants -Pattanayak *et al.* 2013) are some examples.

Solvent extracted parts of many of the reported plants were tested and found to have antimicrobial activities. But in most of the cases, those plants were tested *in vitro* or on the laboratory animals mainly at local applications. On the other hand, in many websites and blogs, it is claimed that part of many plants, natural products etc. are having the power to act as alternative to antibiotics. These include the following plants, plant parts and natural products.

Aloe vera, American goldenseal (*Hydrastis canadensis*), Bearberry (*Uva ursi*), Blue flag root (*Iris versicolor*), Burdock (*Arctiuml appa*), Cayenne Pepper (*Capsicum annuum*), Chaparral (*Larrea tridentata*), Cloves (*Syzygium aromaticum*), Cryptolepis (*Cryptolepis sanguinolenta*), Echinacea (*E. purpurea* and *E. augustifolia*), Eucalyptus (*Eucalyptus globules)* oil, Garlic (*Allium sativum*), Ginger (*Zingiber officinale*), Grapefruit (*Citrus paradisi*) seed extract, Holy thistle (*Cnicus benedictus*), Honey, Horseradish (*Armoracia rusticana*), Juniper (*Juniperus communis*), Licorice (*Glycyrrhiza glabra* and *G. uralensis*), Lobelia (*Lobelia cardinalis*), Mullein (*Verbascum thapsus*), Myrrh (*Commiphora myrrha*), Nasturtium (*Tropaeolum majus, T. peregrinum* and *T. speciosum*), Oregano Oil (*Origanum vulgare*), Poke root (*Phytolacca decandra*), Red clover (*Trifolium pretense*), Sage (*Salvia officinalis*), Thyme (*Thymus vulgaris*), Usnea (*Usnea spp.*), Wild indigo *(Baptisia australis*), Wild thyme (*Thymus serpyllum*), Wormwood (*Artemisia absinthium*), Cranberry (*Vaccinium oxycoccos, V. macrocarpon*) juice (foodmaster.com), Sida (*Sida acuta*), Alchornea (*Alchornea cordifolia*), Bidens (*Bidens pilosa*), Artemisia (*Artemisia annua*), Black pepper (*Piper nigrumand, P. longum*) (Buhner 2011), Olive (*Olea europaea*) leaf extract, Yin Chiao (Chinese Herbal Remedies), Epi Cor (dried fermentate of *Saccharomyces cerevisiae*), Elder berries (*Sambucus nigra*) (Mindell and Hopkins 2009), Coconut (*Cocos nucifera*) Oil, *Forsythia suspensa* (Sisson 2011). Oregon Grape (*Berberis aquifolium*), *Andrographis paniculata*, Manuka honey (European honey bees foraging on *Leptospermum scoparium*) (LoGiudice 2011), Onion (*Allium cepa*), Turmeric (*Curcuma longa*), Cinnamon (*Cinnamomum verum*) , Cardamon (*Elettaria cardamomum*), oils of Basil (*Ocimum basilicum*) and Lavender (*Lavandula angustifolia*) (Harrington 2015), Pau d'Arco (*Tabebuia impetiginosa*) tea, (www.naturalsociety.com), Propolis (Bee glue), Sangre de Drago (bright red resin of *Croton lechleri*) (Stephanie 2015) etc.

The antimicrobial chemicals developed in various species of plants are also a part of evolutionary outcome of the struggle for their existence. It can be assumed that the mechanism of actions of the antibacterial substances of herbal or other uncommon origin is different than the presently used anti microbial substances. So it can be expected that the targeted micro organisms will have to get accustomed with such diverse types of molecules before developing resistance as a part of their struggle for their existence.

Even if we can get success in overcoming the dominance of infective organisms, the following points demand more serious consideration for prevention of repetition of development of such crucial conditions in future.

i) A change is required in our consideration of antibacterial substances as an alternative of the minimum disease protective requirements like good hygienic practices, adequate public health awareness, creation of micro organism free apparatus and environment in the institutions delivering medical supports to the patients, unhealthy surroundings of human dwellings and habitations etc. As an example, it can be said that change of poor living conditions and unhygienic environment of

the slums should be considered far more important rather than the use of anti microbial substances to treat the preventable bacterial diseases of the slum dwellers.

ii) Reconsideration is needed in the fields like use of same antimicrobial substances in different species of animals, birds, fishes etc. for treatment of diseases as well as use of those in agricultural or horticultural operations to control microbial infections. Some anti-microbials may be considered as 'stock' for every species of animals and plants.

iii) As some alternative, maximum efforts may be given to use biological resources and to make provision of biological controls. Different medicinal plants/ plant extracts may be used for curing of ailments of herbivorous animals. Toxic plant parts or their component may be studied to use as biological medicines in agriculture and horticulture. Elaborative research targeting such goal is needed.

iv) Maintenance of proper hygienic practices and nutrition level, decrease in the rate of entry of different types of toxins in the body directly through food or indirectly through food chain, immunization and immune stimulation through herbal medication may be strengthened to reduce the pressure of use of antimicrobial substances in every related sector.

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